Synthesis of a Fragment A Derivative of an Antibiotic, Nosiheptide

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Two 4-ethoxycarbonyl thiazolyl groups were introduced into 2- and 5-positions of 3-hydroxypyridine in 8 steps using 5-cyano-3-hydroxypyridine (**2**) as the starting material. The pyridine derivative obtained in the last step was converted to a fragment A derivative (**21**) by stepwise introduction of the 2-substituted 4-thiazolyl group into the 6-position. The total yield for the formation of **21** via 14 steps was 7.6%.

A polythiazole antibiotic, nosiheptide,[1] (Fig. 1) is composed of heterocyclic fragments C, D, E, A, L-threonine, and dehydroalanine. For a total synthesis of nosiheptide, we have already reported the syntheses of fragments C,[2] D,[3] E,[4] and their peptides.[5] A fragment A derivative can be obtained as a stable compound by acid hydrolysis[1b] of the antibiotic, so that 6-{2-[1-(*t*-butoxycarbonylamino)-2-(*p*-methoxybenzylthio)ethyl]-4-thiazolyl}-3-ethoxy-2,5-bis-(4-ethoxycarbonyl-2-thiazolyl)pyridine (**21**) might be useful as its building block.[6] Thus, we herewith describe the synthesis of **21** in detail.

Similar fragment derivatives of antibiotic micrococcin P and sulfomycin, micrococcinic acid[7] and dimethyl sulfomycinamate,[8] have been recently synthesized using the palladium-catalyzed reaction by cross-coupling between the pyridine and thiazole rings. However, both fragment derivatives are unstable under the conditions of the acid hydrolysis, and the yield for this cross-coupling reaction is not sufficiently high. Therefore, they can not be used for the total synthesis. From the considerations of the stability for the building block and the yield during its formation, we have chosen a stepwise construction method, as shown in the retrosynthesis. (Scheme 1)

Results and Discussion

Because the central ring is 3-hydroxypyridine, 5-bromo-3-hydroxypyridine (**1**)[9] obtained from 2-(aminomethyl)furan was reacted with copper(I) cyanide in *N*,*N*-dimethylformamide (DMF) to give the corresponding 5-cyanide (**2**) in 85% yield, and (**3**) produced by *O*-ethylation of **2** with diethyl sulfate was converted to the thioamide (**4**) by treatment

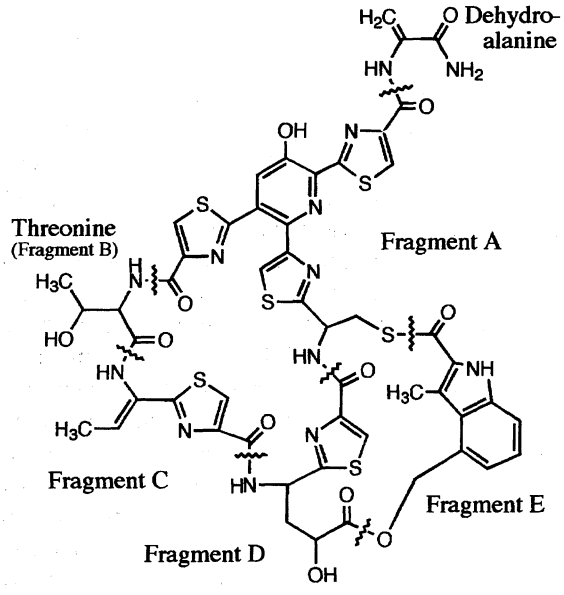


Fig. 1. Structure of nosiheptide.

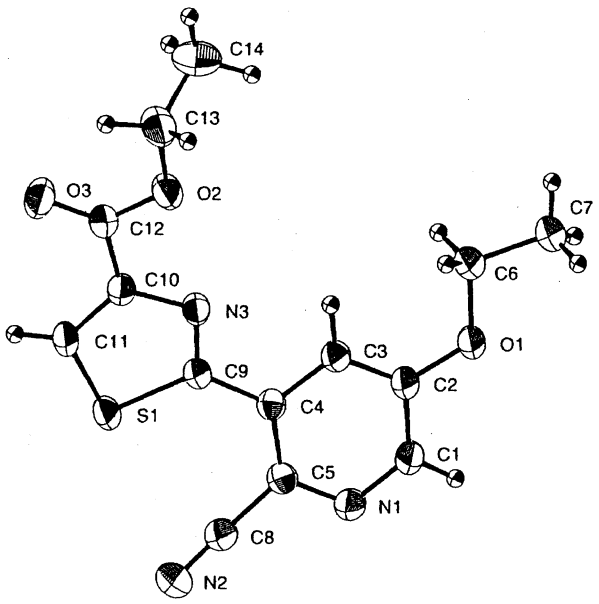
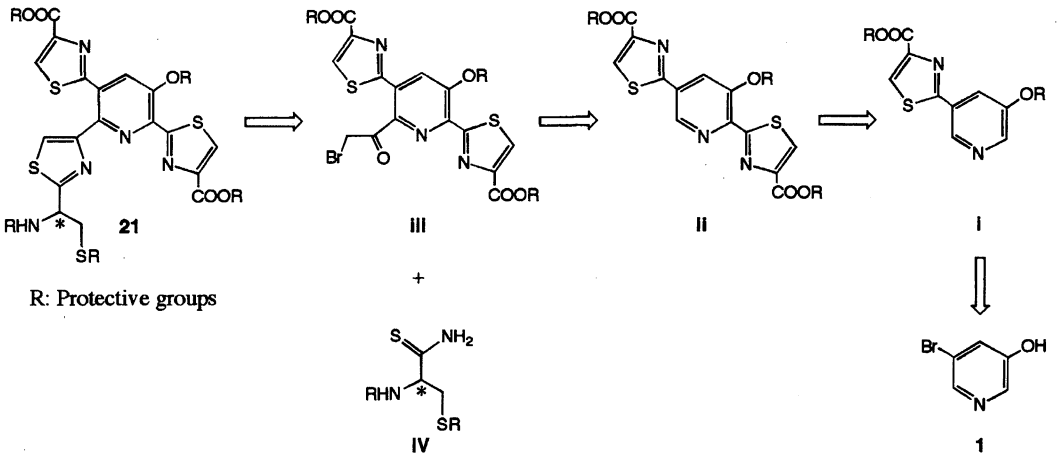
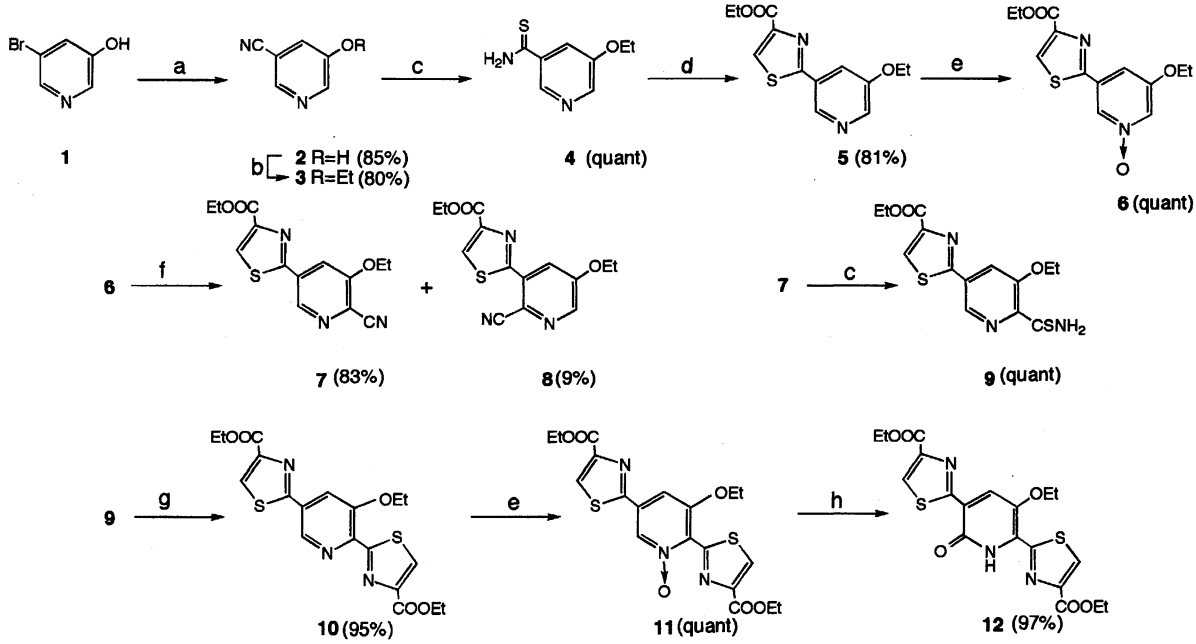


Fig. 2. ORTEP drawing of the molecular structure of 6-isomer **8**.



Scheme 1. Retrosynthesis of **21**.



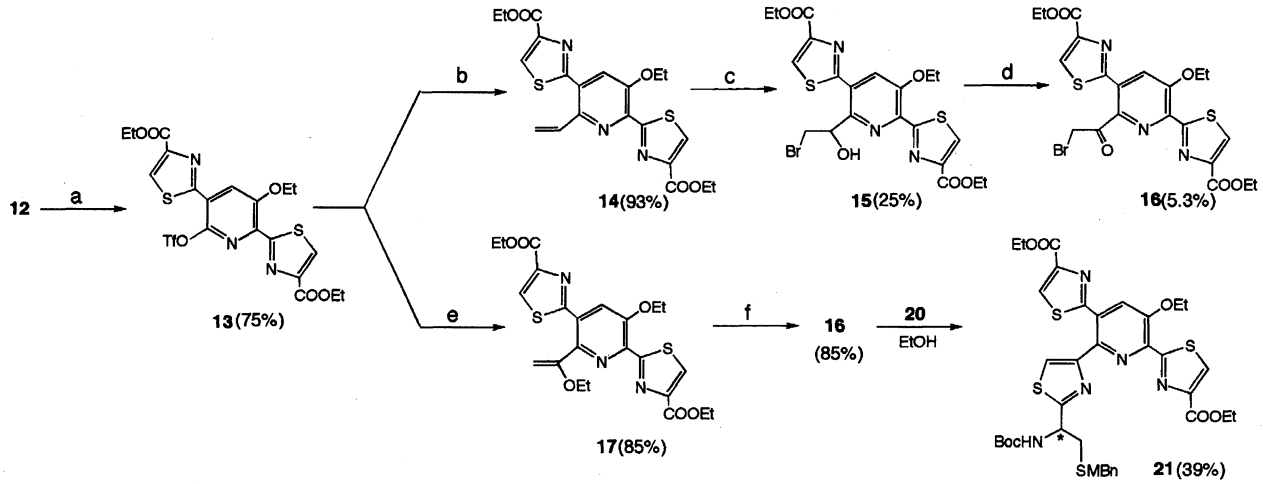
Reagents and conditions: a) CuCN/DMF, b) Et_2SO_4-K_2CO_3/DMF, c) H_2S/Py-Et_3N, d) $BrCH_2COCOOEt$/EtOH, e) *m*-CPBA/CH_2Cl_2, f) TMSCN-Et_3N/MeCN, g) 1:$BrCH_2COCOOEt$ -K_2CO_3/THF, 2:TFAA-Py/THF, h) Ac_2O.

Scheme 2.

with hydrogen sulfide in 80% yield. Condensation of **4** with ethyl bromopyruvate by the Hantzsch method[10] gave the 5-(2-thiazolyl) derivative (**5**) in 81% yield. For the introduction of the second thiazolyl group to the 2-position of the pyridine ring by the Reissert method,[11] **5** was converted to the corresponding *N*-oxide (**6**) with *m*-chloroperbenzoic acid (*m*-CPBA) and then treatment with trimethylsilyl cyanide[12] gave the corresponding two isomers (**7** and **8**) in 83 and 9% yields, respectively. Fortunately, X-ray analysis[13] indicated that the minor product **8** is 6-cyano isomer, as shown in Fig. 2, and, therefore, the major product must be the desired 2-cyano isomer **7**. This result indicates that the intermediate pyridinium cation produced from *O*-silylation may have the main positive charge at the 2-position due to the electron-donating nature of the 3-ethoxy group.

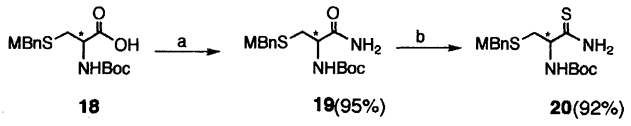
By the modified Hantzsch method,[14] **7** was converted to the second thiazolyl group via the corresponding thioamide (**9**), to give the 2,5-bis(2-thiazolyl) derivative (**10**). For the construction of the C–C bond at the 6-position of **10**, it was converted to the corresponding *N*-oxide (**11**) which, on treatment with acetic anhydride, led directly to the corresponding 6-pyridone (**12**) in 97% yield (Scheme 2).

For the activation of **12**, it was converted to the 6-triflate (**13**) in 75% yield by treatment with trifluoromethanesulfonic anhydride (Tf_2O), in the presence of 4-dimethylaminopyridine (DMAP) and *N*,*N*-diisopropylethylamine. The coupling reaction of **13** with tributyl(vinyl)stannane[15] in the presence of the tetrakis(triphenylphosphine)palladium(0) [$Pd(PPh_3)_4$] and lithium chloride under argon atmosphere gave the corresponding 6-vinyl derivative (**14**) in 93% yield; however, its subsequent conversion into the 6-(2-bromo-1-hydroxy)ethyl group (**15**) with *N*-bromosuccinimide (NBS) and then with MnO_2 into the desired 6-(bromoacetyl) group (**16**) gave poor results, 25 and 5.3% yields, respectively.



Reagents and conditions: a) Tf_2O-*i*-Pr_2NEt/DMAP-CH_2Cl_2, b) $H_2C{=}CHSnBu_3$, $Pd(PPh_3)_4$, LiCl, c) NBS/DMSO-H_2O, d) MnO_2/CH_2Cl_2, e) $CH_2{=}C(OEt)SnBu_3$-$Pd(AcO)_2$-dppp-Et_3N/DMF, f) NBS/THF-H_2O.

Scheme 3.



Reagents and conditions: a) i. HOSu-DCC, ii. *aq*.NH_3, b) Lawesson's reagent/CH_2Cl_2.

Scheme 4.

Therefore, the coupling reaction was carried out with tributyl(1-ethoxyvinyl)stannane[16] in the presence of palladium(II) acetate, 1,3-bis(diphenylphosphino)propane (dppp), under similar conditions, and we obtained the corresponding 1-ethoxyvinyl derivative (**17**) in 85% yield. This was easily converted into **16** with NBS in 85% yield (Scheme 3).

On the other hand, *N*-*t*-butoxycarbonyl-*S*-*p*-methoxybenzyl-L-cysteine (**20**) was synthesized from *N*-Boc-*S*-MBn-Cys (**18**)[17] via the corresponding amide (**19**) by the usual method,[18] in 87% yield (Scheme 4).

Finally, the condensation of **16** and **20** gave the fragment A derivative (**21**) in 39% yield. Further work on the total synthesis of nosiheptide is now under way in our laboratory, using the thus-prepared building blocks.

Experimental

All of the melting points are uncorrected. NMR spectra were measured in $CDCl_3$ solution unless otherwise noted, and the chemical shifts were given in ppm. Both ^1H NMR (tetramethylsilane as an internal standard) and ^{13}C NMR ($CDCl_3$ as an internal standard) spectra were measured on a JEOL GSX 270 spectrometer. Mass spectra (MS) by the electron ionization (EI) technique were obtained on the JEOL JMS-AX505H spectrometer. IR spectra were obtained on a JASCO FT/IR-8000S spectrophotometer. Specific rotations were measured with JASCO DIP-370 polarimeter. Column chromatography was performed on a silica-gel column with Wako gel C-300.

5-Cyano-3-hydroxypyridine (2). A solution of 5-bromo-3-hydroxypyridine (4.70 g, 27 mmol) and Cu(I)CN (3.70 g, 41.3 mmol) in DMF (10 ml) was heated under reflux for 4 h and then concentrated. To the residue was added saturated aqueous ammonia solution (10 ml), and the mixture was caused to bubble by a stream of ammonia gas for 1 h. Then the solution was adjusted to pH 4 with concd HCl (30 ml), and then filtered. The filtrate was extracted with ethyl acetate (100 ml×3) and the usual workup of extracts gave a crude product. An additional crop was also obtained by extraction of the residue with the same solvent. Combined crude products were purified on silica-gel (hexane–ethyl acetate, 1 : 1) to give pure **2** (2.78 g; 86%), as a pale yellow powder. Mp 239.0—240.2 °C; MS *m/z* 121 ($M+1^+$); IR (KBr) 3450 (OH), 2240 cm^{-1} (CN); ^1H NMR (DMSO-d_6) δ = 7.59 (dd, 1H, *J* = 2.0, 3.0 Hz, H-4), 8.41 (d, 1H, *J* = 3.0 Hz, H-2), 8.46 (d, 1H, *J* = 2.0 Hz, H-6), 10.8 (br-s, 1H, OH); ^{13}C NMR (DMSO-d_6) δ = 109.3 (C-5), 117.0 (CN), 124.8 (C-4), 142.6 (C-2), 142.9 (C-6), 153.5 (C-3). Found: C, 59.95; H, 3.40; N, 23.28%. Calcd for $C_6H_4N_2O$: C, 60.00; H, 3.36, N, 23.32%.

5-Cyano-3-ethoxypyridine (3). To a solution of **2** (1.07 g, 8.91 mmol) and anhydrous K_2CO_3 (1.85 g, 13.4 mmol) in DMF (20 ml) was added diethyl sulfate (0.82 g, 5.34 mmol) under vigorous stirring, and the resulting solution was heated under reflux for 5 h, and extracted with ethyl acetate (150 ml×2). The combined extracts were washed with saturated $NaHCO_3$ (100 ml) and H_2O (100 ml×2) and dried with $MgSO_4$. The residue obtained by evaporation of the solvent was chromatographed on silica-gel (hexane–ethyl acetate, 5 : 1) to give **3** (1.06 g; 80%), as a pale yellow powder. Mp 100—101 °C; MS *m/z* 148 (M^+); IR (KBr) 3090 and 2990 (C–H), 2230 cm^{-1} (CN); ^1H NMR (DMSO-d_6) δ = 1.48 (t, 3H, *J* = 6.9 Hz, CH_3), 4.11 (q, 2H, *J* = 6.9 Hz, CH_2O), 7.38 (dd, 1H, *J* = 1.5, 3.0 Hz, H-4), 8.47 (d, 1H, *J* = 1.5 Hz, H-6), 8.49 (d, 1H, *J* = 3.0 Hz, H-2); ^{13}C NMR (DMSO-d_6) δ = 14.2 (CH_3), 64.3 (CH_2O), 109.8 (C-5), 116.4 (CN), 124.8 (C-4), 142.4 (C-2), 144.1 (C-6), 154.4 (C-3). Found: C, 64.81; H, 5.50; N, 18.85%. Calcd for $C_8H_8N_2O$: C, 64.85; H, 5.44, N, 18.91%.

3-Ethoxy-5-thiocabamoylpyridine (4). A solution of **3** (1.46 g, 9.85 mmol) in pyridine (10 ml) and Et_3N (4.98 g, 49.2 mol) was caused to bubble by a stream of H_2S gas for 1 h. The residue obtained by evaporation of the solvent was chromatographed on silica-gel (hexane–ethyl acetate, 1 : 2) to give **4** (1.80 g), as a yellow powder in quantitative yield. Mp 121.5—122 °C; MS *m/z* 182 (M^+); IR (KBr) 3350 and 3250 (NH_2), 3070 and 2290, 1460 cm^{-1} (C=S); ^1H NMR (DMSO-d_6) δ = 1.37 (t, 3H, *J* = 7.8 Hz, CH_3), 4.16 (q, 2H, *J* = 7.8 Hz, CH_2O), 7.75 (q, 1H, *J* = 1.5, 2.7 Hz, H-4), 8.39 (d, 1H, *J* = 2.7 Hz, H-2), 8.65 (d, 1H, *J* = 1.5 Hz, H-6), 9.71 and 10.11 (each br-s, 2H, NH_2); ^{13}C NMR (DMSO-d_6) δ = 14.5 (CH_3),

63.9 (CH_2O), 119.1 (C-4), 135.6 (C-5), 139.9 (C-2), 140.0 (C-6), 153.9 (C-3), 197.4 ($CSNH_2$). Found: C, 52.66; H, 5.59; N, 15.33%. Calcd for $C_8H_{10}N_2OS$: C, 52.73; H, 5.53, N, 15.37%.

3-Ethoxy-5-(4-ethoxycarbonyl-2-thiazolyl)pyridine (5). To an ice-cooled solution of **4** (0.90 g, 4.94 mmol) in ethanol (10 ml) was added dropwise a solution of ethyl bromopyruvate (1.56 g, 8.00 mmol) in ethanol (5 ml) for 15 min, and the resulting solution was kept at room temperature for 2 h, heated under reflux for 5 h, and then evaporated. The residue was extracted with ethyl acetate (100 ml×2), and the combined extracts were washed with saturated $NaHCO_3$ solution (50 ml), H_2O (50 ml×2), dried with $MgSO_4$, and then evaporated. The residue was chromatographed on silica-gel (hexane–ethyl acetate, 1 : 1) to give **5** (1.11 g; 81%), as a white powder. Mp 68—69 °C; MS *m/z* 277 ($M-1^+$); IR (neat) 3100 and 2990 (C–H), 1710 cm^{-1} (C=O); ^1H NMR δ = 1.45 (t, 3H, J = 7.2 Hz, CH_3-ester), 1.47 (t, 3H, J = 7.0 Hz, CH_3-ether), 4.18 (q, 2H, J = 7.0 Hz, CH_2O-ether), 4.43 (q, 2H, J = 7.2 Hz, CH_2O-ester), 7.86 (t, 1H, J = 2.0, 2.5 Hz, Py-4), 8.22 (bs, 1H, Th-5), 8.38 (d, 1H, J = 2.5 Hz, Py-6), 8.73 (d, 1H, J = 2.0 Hz, Py-2); ^{13}C NMR δ = 14.1 (CH_3-ester), 14.4 (CH_3-ether), 61.4 (CH_2O-ester), 64.1 (CH_2O-ether), 117.5 (Py-4), 127.5 (Th-5), 129.1 (Py-5), 139.6 (Py-2), 140.5 (Py-6), 148.1 (Th-4), 155.0 (Py-3), 160.9 (Th-2), 165.0 (C=O). Found: C, 55.92; H, 5.17; N, 9.94%. Calcd for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07, N, 10.06%.

3-Ethoxy-5-(4-ethoxycarbonyl-2-thiazolyl)pyridine *N*-Oxide (6). To a solution of **5** (1.0 g, 3.59 mmol) in CH_2Cl_2 (10 ml) was added 70% *m*-CPBA (1.33 g, 5.39 mmol), and the mixture was stirred for 2 h at room temperature and concentrated. The residue was extracted with ether (50 ml×2). The usual treatment of the combined extracts gave the crude product, which was purified on silica-gel ($CHCl_3$–EtOH, 20 : 1) to give pure **6** (1.06 g), as a white powder in quantitative yield. Mp 123.5—125.5 °C; MS *m/z* 293 ($M-1^+$); IR (KBr) 3050 and 3000 (C–H), 1710 (C=O), 1590 cm^{-1} (N→O); ^1H NMR δ = 1.44 (t, 3H, J = 7.2 Hz, CH_3-ester), 1.47 (t, 3H, J = 6.9 Hz, CH_3-ether), 4.15 (q, 2H, J = 6.9 Hz, CH_2O-ether), 4.46 (q, 2H, J = 7.2 Hz, CH_2O-ester), 7.51 (br-t, 1H, J = 1.5, 2.0 Hz, Py-4), 8.00 (br-t, 1H, J = 1.5, 2.0 Hz, Py-6), 8.26 (s, 1H, Th-5), 8.47 (t, 1H, J = 1.5 Hz, Py-2); ^{13}C NMR δ = 14.1 (CH_3-ester), 14.3 (CH_3-ether), 61.6 (CH_2O-ester), 65.2 (CH_2O-ether), 110.6 (Py-4), 128.3 (Th-5), 129.1 (Py-6), 130.4 (Py-2), 131.5 (Py-5), 148.5 (Th-4), 157.2 (Py-3), 160.7 (Th-2), 162.3 (C=O). Found: C, 52.89; H, 4.92; N, 9.37%. Calcd for $C_{13}H_{14}N_2O_4S$: C, 53.05; H, 4.79, N, 9.52%.

2-Cyano-3-ethoxy-5-(4-ethoxycarbonyl-2-thiazolyl)pyridine (7). A solution of **6** (107 mg, 0.36 mmol), Et_3N (109 mg, 1.08 mmol) and TMSCN (107 mg, 1.08 mmol) in acetonitrile (5 ml) was heated under reflux for 8 h, and then the solvent was evaporated. The residue was extracted with CH_2Cl_2 (25 ml×3), and the combined extracts were washed with water (15 ml×2), dried over anhydrous Na_2SO_4, and then concentrated in vacuo to give the crude product, which was separated on silica-gel (hexane–ethyl acetate, 2 : 1) into **7** (84 mg; 83%) and **8** (9 mg; 9%) regioisomers as white powders. Mp 158—159 °C; MS *m/z* 302 ($M-1^+$); IR (KBr) 3100 and 2990 (C–H), 2230 (CN), 1710 cm^{-1} (C=O); ^1H NMR δ = 1.45 (t, 3H, J = 7.2 Hz, CH_3-ester), 1.56 (t, 3H, J = 7.0 Hz, CH_3-ester), 4.33 (q, 2H, J = 7.0 Hz, CH_2O-ether), 4.48 (q, 2H, J = 7.2 Hz, CH_2O-ester), 8.04 (d, 1H, J = 1.7 Hz, Py-4), 8.33 (s, 1H, Th-5), 8.74 (d, 1H, J = 1.7 Hz, Py-6); ^{13}C NMR δ = 14.3 (CH_3-ester), 14.4 (CH_3-ether), 61.8 (CH_2O-ester), 65.7 (CH_2O-ether), 114.7 (CN), 116.9 (Py-2,4), 128.8 (Th-5), 132.5 (Py-5), 140.2 (Py-6), 148.8 (Th-4), 158.0 (Py-3), 160.8 (Th-2), 163.1 (C=O). Found: C, 55.39; H, 4.41; N, 13.61%. Calcd for $C_{14}H_{13}N_3O_3S$: C, 55.44; H, 4.32, N, 13.85%.

6-Cyano-3-ethoxy-5-(4-ethoxycarbonyl-2-thiazolyl)pyridine (8). Mp 159.5—160.5 °C; MS *m/z* 302 ($M-1^+$); IR (KBr) 3100 and 3000 (C–H), 2220 (CN), 1720 cm^{-1} (C=O); ^1H NMR δ = 1.49 (t, 3H, J = 7.2 Hz, CH_3-ester), 1.55 (t, 3H, J = 6.9 Hz, CH_3-ether), 4.26 (q, 2H, J = 6.9 Hz, CH_2O-ether), 4.48 (q, 2H, J = 7.2 Hz, CH_2O-ester), 7.99 (d, 1H, J = 2.5 Hz, Py-4), 8.39 (s, 1H, Th-5), 8.43 (d, 1H, J = 2.5 Hz, Py-2); ^{13}C NMR δ = 14.2 (CH_3-ester), 14.3 (CH_3-ether), 61.8 (CH_2O-ester), 65.0 (CH_2O-ether), 116.8 (CN), 119.2 (Py-4), 121.5 (Py-6), 129.6 (Th-5), 134.3 (Py-5), 141.7 (Py-2), 148.0 (Th-4), 157.2 (Py-3), 160.8 (Th-2), 169.3 (C=O). Found: C, 55.40; H, 4.45; N, 12.95%. Calcd for $C_{14}H_{13}N_3O_3S$: C, 55.44; H, 4.32, N, 13.85%.

3-Ethoxy-5-(4-ethoxycarbonyl-2-thiazolyl)-2-pyridinethiocarboxamide (9). A solution of **7** (366 mg, 1.21 mmol) in pyridine (5 ml) and Et_3N (612 mg, 6.05 mmol) was caused to bubble by a stream of H_2S gas for 4 h. The residue obtained by evaporation of the solvent was chromatographed on silica-gel (hexane–ethyl acetate, 1 : 2) to give **9** (408 mg), as a yellow powder in quantitative yield. Mp 183.5—184.5 °C; MS *m/z* 336 ($M-1^+$); IR (KBr) 3300 and 3150 (NH_2), 3000 and 2900 (C–H), 1710 (C=O), 1450 cm^{-1} (C=S); ^1H NMR (DMSO-d_6) δ = 1.35 (t, 3H, J = 7.2 Hz, CH_3-ester), 1.38 (t, 3H, J = 6.7 Hz, CH_3-ether), 4.25 (q, 2H, J = 6.7 Hz, CH_2O-ether), 4.37 (q, 2H, J = 7.2 Hz, CH_2O-ester), 7.90 (d, 1H, J = 1.2 Hz, Py-4), 8.67 (d, 1H, J = 1.2 Hz, Py-6), 8.69 (s, 1H, Th-5), 9.77 and 10.22 (each br-s, 2H, NH_2); ^{13}C NMR (DMSO-d_6) δ = 14.3 (CH_3-ester), 14.5 (CH_3-ether), 61.1 (CH_2O-ester), 64.7 (CH_2O-ether), 117.3 (Py-4), 129.1 (Py-5), 130.4 (Th-5), 137.7 (Py-6), 147.1 (Th-4), 150.2 (Py-3), 150.5 (Py-2), 160.6 (Th-2), 164.3 (C=O), 198.0 (C=S). Found: C, 49.47; H, 4.71; N, 11.83%. Calcd for $C_{14}H_{15}N_3O_3S_2$: C, 49.84; H, 4.48, N, 12.45%.

3-Ethoxy-2,5-bis(4-ethoxycarbonyl-2-thiazolyl)pyridine (10). To an ice-cooled solution of **9** (100 mg, 0.3 mmol) and $KHCO_3$ (240 mg, 2.40 mmol) in THF (3 ml) was added dropwise under stirring a solution of ethyl bromopyruvate (88.0 mg, 0.45 mmol) in THF (5 ml) for 5 min under argon atmosphere, and then the stirring was continued for 2 h at room temperature. To the ice-cooled reaction mixture was further added dropwise a mixture of TFAA (285 mg, 1.01 mmol), pyridine (186 mg, 2.35 mmol) and THF (3 ml), and the mixture was stirred for 1 h, then concentrated. The residue was extracted with CH_2Cl_2 (20 ml×3), and the combined extracts were washed with water (10 ml×2), dried over $MgSO_4$, and evaporated. The residual product was purified on silica-gel (hexane–ethyl acetate, 1 : 2) to give **10** (124 mg; 95%) as a pale yellow powder. Mp 167—168 °C; MS *m/z* 432 ($M-1^+$); IR (KBr) 3100 and 3000 (C–H), 1725 and 1705 cm^{-1} (C=O); ^1H NMR δ = 1.45 (t, 6H, J = 6.9 Hz, CH_3-ester×2), 1.67 (t, 3H, J = 6.9 Hz, CH_3-ether), 4.39—4.51 (m, 6H, CH_2O×3), 8.11 (d, 1H, J = 1.5 Hz, Py-4), 8.28 and 8.36 (each s, 1H×2, Th-5×2), 8.84 (d, 1H, J = 1.5 Hz, Py-6); ^{13}C NMR (δ = 14.2 (CH_3×2-ester), 14.5 (CH_3-ether), 61.3 and 61.6 (CH_2O-ester), 65.6 (CH_2O-ether), 117.3 (Py-4), 128.0 and 129.3 (Th-5×2), 130.2 (Py-5), 139.7 (Py-6), 140.8 (Py-2), 147.8 and 148.4 (Th-4×2), 152.8 (Py-3), 160.1 and 161.7 (Th-2×2), 163.5 and 164.2 (C=O×2). Found: C, 52.55; H, 4.50; N, 9.53%. Calcd for $C_{19}H_{19}N_3O_5S_2$: C, 52.64; H, 4.42, N, 9.69%.

3-Ethoxy-2,5-bis(4-ethoxycarbonyl-2-thiazolyl)pyridine *N*-Oxide (11). To a solution of **10** (527 mg, 1.22 mmol) in CH_2Cl_2 (10 ml) was added 70% *m*-CPBA (330 mg, 1.34 mmol), and the mixture was stirred for 2 h at room temperature. After dilution with Et_2O, insoluble impurities were removed on a short column, and then the solution was concentrated to give the crude product, which was purified on silica-gel (hexane–ethyl acetate, 1 : 2) to give pure **11** (547 mg), as a white powder in quantitative yield. Mp 215—216

°C; MS *m/z* 448 ($M-1^+$); IR (KBr) 3100 and 2900 (C–H), 1740 and 1715 cm^{-1} (C=O); ^1H NMR δ = 1.46 (t, 6H, *J* = 7.2 Hz, CH_3-ester×2), 1.73 (t, 3H, *J* = 6.9 Hz, CH_3-ether), 4.40—4.52 (m, 6H, CH_2O×3), 7.76 (d, 1H, *J* = 1.5 Hz, Py-4), 8.31 and 8.41 (each s, 1H×2, Th-5×2), 8.67 (d, 1H, *J* = 1.5 Hz, Py-6); ^{13}C NMR δ = 14.2 (CH_3-ester×2), 14.3 (CH_3-ether), 61.3 and 61.8 (CH_2O-ester), 66.8 (CH_2O-ether), 108.4 (Py-4), 128.7 and 129.3 (Th-5×2, Py-2), 129.6 (Py-6), 133.7 (Py-5), 146.9 and 148.7 (Th-4×2), 154.0 (Py-3), 156.1 and 160.6 (Th-2×2), 161.7 and 161.9 (C=O×2). Found: C, 50.59; H, 4.33; N, 9.16%. Calcd for $C_{19}H_{19}N_3O_6S_2$: C, 50.77; H, 4.26, N, 9.35%.

3- Ethoxy- 2, 5- bis(4- ethoxycarbonyl- 2- thiazolyl)- 6(1*H*)-pyridone (12). A mixture of **11** (50 mg, 0.11 mmol) and acetic anhydride (3 ml) was heated at 100 °C for 2 h. After the acetic anhydride was removed in vacuo, the resulting crude product was purified by silica-gel (hexane–ethyl acetate, 1 : 2) to give **12** (49 mg; 97%), as a yellow powder. Mp 229—231 °C; MS *m/z* 448 ($M-1^+$); IR (KBr) 3360 (NH), 3100 and 3000 (C–H), 1705 (C=O), 1655 cm^{-1} (CONH); ^1H NMR δ = 1.45 (t, 6H, *J* = 7.2 Hz, CH_3-ester×2), 1.59 (t, 3H, *J* = 6.9 Hz, CH_3-ether), 4.38—4.49 (m, 6H, CH_2O×3), 8.30 and 8.33 (each s, 1H×2, Th-5×2), 8.72 (d, 1H, *J* = 1.5 Hz, Py-4), 10.56 (br-s, 1H, NH); ^{13}C NMR δ = 14.3 (CH_3×2-ester), 15.0 (CH_3-ether), 61.4 and 61.7 (CH_2O-ester), 67.5 (CH_2O-ether), 124.9 (Py-5), 125.0 (Py-2), 127.5 (Py-4), 129.9 and 130.0 (Th-5×2), 140.9 (Py-3), 146.4 and 148.7 (Th-4×2), 154.7 (Py-6), 157.0 and 160.2 (Th-2×2), 160.9 and 161.6 (C=O×2). Found: C, 50.81; H, 4.37; N, 9.09%. Calcd for $C_{19}H_{19}N_3O_6S_2$: C, 50.77; H, 4.26, N, 9.35%.

3-Ethoxy-2,5-bis(4-ethoxycarbonyl-2-thiazolyl)-6-trifluoromethylsulfonyloxypyridine (13). To a solution of **12** (66 mg, 0.15 mmol), DMAP (3.7 mg, 0.03 mmol), and $(i\text{-Pr})_2$NEt (77.6 mg, 0.60 mmol) in CH_2Cl_2 (3 ml), was added Tf_2O (42.3 mg, 0.15 mmol) with stirring under argon atmosphere. The stirring was continued overnight at room temperature, then the mixture was extracted with CH_2Cl_2 (25 ml×3). The combined extracts were washed with saturated $NaHCO_3$ (10 ml×2) and water (10 ml), dried with Na_2SO_4, and concentrated. The remained product was purified on silica-gel (hexane–ethyl acetate, 2 : 1) to give **13** (65 mg; 75%) as a pale yellow powder. Mp 168.5—169.5 °C; MS *m/z* 580 ($M-1^+$); IR (KBr) 3100 and 3000 (C–H), 1725 and 1710 (C=O), 600 cm^{-1} (C–F); ^1H NMR δ = 1.45 (t, 6H, *J* = 6.9 Hz, CH_3-ester×2), 1.68 (t, 3H, *J* = 6.9 Hz, CH_3-ether), 4.41—4.52 (m, 6H, CH_2O×3), 8.36 and 8.39 (each s, 1H×2, Th-5×2), 8.52 (s, 1H, Py-4); ^{13}C NMR δ = 14.0 and 14.1 (CH_3-ester), 14.3 (CH_3-ether), 61.3 and 61.6 (CH_2O-ester), 66.4 (CH_2O-ether), 120.8 (CF_3), 121.2 (Py-5), 123.7 (Py-4), 129.9 and 130.0 (Th-5×2), 137.4 (Py-2), 143.6 (Py-6), 147.7 and 148.5 (Th-4×2), 152.4 (Py-3), 158.2 and 160.7 (Th-2×2), 161.2 and 162.9 (C=O×2). Found: C, 41.18; H, 3.25; N, 7.04%. Calcd for $C_{20}H_{18}F_3N_3O_8S_3$: C, 41.31; H, 3.12, N, 7.23%.

3-Ethoxy-2,5-bis(4-ethoxycarbonyl-2-thiazolyl)-6-vinylpyridine (14). To a solution of **13** (81 mg, 0.09 mmol) in THF (3 ml) were added $Pd(PPh_3)_4$ (2.3 mg, 2 mol%), LiCl (11.4 mg, 0.27 mmol), and tributyl(vinyl)stannane (28.5 mg, 0.094 mmol) with stirring under argon atmosphere. The resulting mixture was heated under reflux for 22 h, and then concentrated. The residual materials were extracted with CH_2Cl_2 (25 ml×3), and the combined extracts were washed with saturated $NaHCO_3$ (10 ml) and H_2O (10 ml), and evaporated. The remained product was purified on silica-gel (hexane–ethyl acetate, 1 : 1) to give **14** (38.6 mg; 93%) as a syrup. MS *m/z* 458 ($M-1^+$); ^1H NMR δ = 1.45 (t, 6H, *J* = 7.2 Hz, CH_3-ester×2), 1.65 (t, 3H, *J* = 6.9 Hz, CH_3-ether), 4.33 (q, 2H, *J* = 6.9 Hz, CH_2O-ether), 4.43—4.51 (m, 4H, CH_2O), 5.59 (dd, 1H, *J* = 1.9, 10.7 Hz, vinyl), 6.56 (dd, 1H, *J* = 1.9, 16.8 Hz, vinyl), 6.27 (dd, 1H, *J* = 10.7, 16.8 Hz, vinyl), 7.71 (s, 1H, Py-4), 8.33 and 8.35 (each s, 2H, Th-5×2).

6-(2-Bromo-1-hydroxyethyl)-3-ethoxy-2,5-bis(4-ethoxycarbonyl-2-thiazolyl)pyridine (15). To a solution of **14** (156 mg, 0.34 mmol) in DMSO (6 ml) were added H_2O (2 ml) and NBS (121 mg, 0.68 mmol). The mixture was stirred for 10 min under argon atmosphere, and then concentrated. The residue was extracted with ethyl acetate (50 ml×2), and the combined extracts were washed with water (20 ml×3), dried with Na_2SO_4, and then evaporated. The product was purified on silica-gel (hexane–ethyl acetate, 1 : 1) to give **15** (65 mg; 25%) as a syrup. MS *m/z* 555 (M^+); ^1H NMR δ = 1.49 (t, 6H, *J* = 6.9 Hz, CH_3-ester×2), 1.69 (t, 3H, *J* = 6.9 Hz, CH_3-ether), 3.87 (dd, 1H, *J* = 6.6, 10.1 Hz, CHBr), 4.09 (dd, 1H, *J* = 5.3, 10.1 Hz, CHBr), 4.32—4.76 (m, 6H, CH_2O×3), 5.48 (dd, 1H, *J* = 5.3, 6.6 Hz, CHOH), 7.67 (s, 1H, Py-4), 8.33 and 8.34 (each s, 2H, Th-5×2).

6-Bromoacetyl-3-ethoxy-2,5-bis(4-ethoxycarbonyl-2-thiazolyl)pyridine (16). A solution of **15** (30 mg, 0.065 mmol) and NBS (23.1 mg, 0.13 mmol) in DMSO (6 ml) and H_2O (1 ml) was stirred at 0 °C under argon atmosphere for 10 min, and then extracted with ethyl acetate (20 ml×2). The combined extracts were washed with water (10 ml×3), dried with Na_2SO_4, and then concentrated. A solution of the residue and active MnO_2 (199.5 mg, 2.29 mmol) in CH_2Cl_2 (3 ml) was stirred overnight at room temperature, and filtered to remove MnO_2. The filtrate was evaporated, and the residue was purified on silica-gel (hexane–ethyl acetate, 2 : 3) to give **16** (1.9 mg; 5.3%) as a syrup. MS *m/z* 553 (M^+); IR (neat) 3100 and 3000 (C–H), 1725 and 1700 cm^{-1} (C=O); ^1H NMR δ = 1.45 (dt, 6H, *J* = 7.0 Hz, CH_3-ester×2), 1.67 (t, 3H, *J* = 6.9 Hz, CH_3-ether), 4.33—4.51 (m, 6H, CH_2O×3), 4.93 (s, 2H, $BrCH_2$), 7.84 (s, 1H, Py-4), 8.36 and 8.37 (each s, 2H, Th-5×2). Found: C, 45.32; H, 3.86; N, 7.21%. Calcd for $C_{21}H_{20}BrN_3O_6S_2$: C, 45.49; H, 3.64, N, 7.58%.

3-Ethoxy-2,5-bis(4-ethoxycarbonyl-2-thiazolyl)-6-(1-ethoxyvinyl)pyridine (17). A solution of **13** (81 mg, 0.14 mmol), $Pd(OAc)_2$ (3.2 mg, 10 mol%), dppp (5.8 mg, 10 mol%), Et_3N (42.5 mg, 0.42 mmol), tributyl(1-ethoxyvinyl)stannane (139 mg, 0.38 mmol) in DMF (3 ml) was stirred at 60—70 °C for 3 h under argon atmosphere, and then concentrated. The residue was extracted with CH_2Cl_2 (25 ml×3), and the combined extracts were washed with saturated $NaHCO_3$ (10 ml) and water (10 ml), dried with Na_2SO_4, and then evaporated. The residue was purified on silica-gel (hexane–ethyl acetate, 1 : 1) to give **17** (60 mg; 85%) as a syrup. MS *m/z* 502 ($M-1^+$); IR (KBr) 3100 and 3000 (C–H), 1720 cm^{-1} (C=O); ^1H NMR δ = 1.10 (t, 3H, *J* = 6.9 Hz, CH_3 ethoxyvinyl), 1.44 (dt, 6H, *J* = 6.9 Hz, CH_3-ester×2), 1.64 (t, 3H, *J* = 6.9 Hz, CH_3-ether), 3.81 (q, 2H, *J* = 6.9 Hz, CH_2O-vinylethoxy), 4.43—4.51 (m, 7H, CH_2O×3 + vinyl CH), 4.88 (d, 1H, *J* = 2.0 Hz, vinyl CH), 7.94 (s, 1H, Py-4), 8.30 and 8.33 (each s, 2H, Th-5×2); ^{13}C NMR δ = 14.1 (CH_3×2-ester), 14.2 (CH_3-ether×2), 61.2 (CH_2O-ester×2), 61.3 and 65.4 (CH_2O-ether×2), 88.9 (vinyl-CH_2), 122.0 (Py-4) 129.1 and 129.4 (Th-5×2), 129.2 (Py-5), 138.8 (Py-2), 145.0 (Py-6), 146.0 and 148.0 (Th-4×2), 151.2 (Py-3), 158.1 (vinyl-C), 161.0 and 161.5 (Th-2×2), 164.8 and 165.4 (C=O×2). Found: C, 54.52; H, 5.13; N, 7.97%. Calcd for $C_{23}H_{25}N_3O_6S_2$: C, 54.86; H, 5.00, N, 8.34%.

***N*-*t*-Butoxycarbonyl-*S*-4-methoxybenzyl-L-cysteinamide (19).** To an ice-cooled solution of **18** (500 mg, 1.46 mmol) and HOSu (184 mg, 1.60 mmol) in THF (10 ml) was added DCC (330 mg, 1.60 mmol), and the mixture was stirred for 1 h at 0 °C and a further 5 h at room temperature. After the insoluble materials were filtered

off, the filtrate was concentrated in vacuo to give a residue, which was dissolved in ethyl acetate (10 ml). To the resulting solution was added concd aqueous NH_4OH (5 ml) at 0 °C. After being stirred for 30 min at room temperature, the reaction mixture was diluted with ethyl acetate (50 ml). The organic layer was washed with saturated $NaHCO_3$ solution and brine, and dried over anhydrous Na_2SO_4. Evaporation in vacuo gave a residual crude product, which was purified on silica-gel (hexane–ethyl acetate, 4 : 1) to give **19** (472 mg; 95%) as a white powder. Mp 135—136 °C; $[\alpha]_D$ −9.7° (*c* 1.0, MeOH); MS *m/z* 340 (M^+); IR (neat) 3380 and 3320 ($CONH_2$, NH), 2940 (C–H), 1690 and 1640 cm^{-1} (C=O); ^1H NMR δ = 1.46 (s, 9H, *t*-Bu), 2.73 and 2.89 (each dd, 2H, *J* = 6.4, 14.1 Hz, SCH_2), 3.74 (s, 2H, $ArCH_2$), 3.80 (s, 3H, OCH_3), 4.26 (br-d, 1H, CH), 5.30 (br-d, 1H, NH), 5.46 and 6.29 (each br-s, 2H, NH_2), 6.85 and 7.27 (each d, 4H, *J* = 8.7 Hz, Ph); ^{13}C NMR δ = 28.2 (*t*-BuO), 33.3 (SCH_2), 35.8 ($ArCH_2$), 53.2 (CH), 55.2 (OCH_3), 80.3 (*t*-BuO), 113.9 (Ar-3,5), 129.6 (Ar-1), 130.1 (Ar-2,6), 155.4 (CONH), 158.7 (Ar-4), 173.3 ($CONH_2$). Found: C, 56.03; H, 7.47; N, 7.98%. Calcd for $C_{16}H_{24}N_2O_4S$: C, 56.45; H, 7.11, N, 8.23%.

***N*-*t*-Butoxycarbonyl-*S*-4-methoxybenzyl-L-cysteine Thioamide (20).** To a solution of **19** (200 mg, 0.59 mmol) in CH_2Cl_2 (5 ml) was added Lawesson's reagent (1.96 g, 0.48 mmol) and the mixture was stirred for 5 h under argon atmosphere, and then concentrated. The residue was purified on silica-gel (hexane–ethyl acetate, 4 : 1) to give **20** (198 mg; 92%) as a pale yellow syrup. $[\alpha]_D$ −11.4° (*c* 1.0, MeOH); MS *m/z* 356 (M^+); IR (neat) 3310 and 3150 ($CSNH_2$, NH), 2950 (C–H), 1690 (C=O), 1520 cm^{-1} (C=S); ^1H NMR δ = 1.45 (s, 9H, *t*-Bu), 2.84—2.99 (m, 2H, SCH_2), 3.74 (s, 2H, $ArCH_2$), 3.80 (s, 3H, OCH_3), 4.47 (q, 1H, CH), 5.41 (br-d, 1H, NH), 6.85 and 7.27 (each d, 4H, *J* = 6.5 Hz, Ph), 7.52 and 7.68 (each br-s, 2H, NH_2); ^{13}C NMR δ = 28.1 (*t*-BuO), 35.6 (SCH_2), 36.1 ($ArCH_2$), 55.0 (OCH_3), 58.6 (CH), 80.3 (*t*-BuO), 113.7 (Ar-3,5), 129.5 (Ar-1), 129.9 (Ar-2,6), 155.2 (CONH), 158.4 (Ar-4), 206.7 ($CSNH_2$). Found: C, 53.88; H, 6.94; N, 7.52%. Calcd for $C_{16}H_{24}N_2O_3S_2$: C, 53.91; H, 6.79, N, 7.86%.

6-{2-[1-(*t*-Butoxycarbonylamino)-2-(*p*-methoxybenzylthio)-ethyl]-4-thiazolyl}-3-ethoxy-2,5-bis(4-ethoxycarbonyl-2-thiazolyl)pyridine (21). To a solution of **17** (90.0 mg, 0.18 mmol) in THF–H_2O (3 : 1; 4 ml) was added NBS (32.0 mg, 0.18 mmol), and mixture was stirred for 10 min at 0 °C. The reaction mixture was extracted with $CHCl_3$ (25 ml×3), and the combined extracts were washed with water, and then dried over anhydrous Na_2SO_4. Evaporation in vacuo gave a residual crude product, which was dissolved in ethanol (3 ml). To the resulting solution was added ethanol solution of **20** (64.2 mg, 0.18 mmol) at 0 °C. After being stirred for 30 min, and heated under reflux for 1 h, the solution was concentrated to 1/3 volume and extracted with $CHCl_3$ (25 ml×3). The combined extracts were washed with water (10 ml×2), dried over anhydrous Na_2SO_4 and evaporated to give the crude product, which was purified on a silica-gel (hexane–ethyl acetate, 1 : 1) to give **21** (48.2 mg) as a syrup in 33% yield from **17**. $[\alpha]_D$ −13.9° (*c* 1.05, MeOH); MS (FAB matrix, 3-nitrobenzyl alcohol) *m/z* 812 (M^+); IR (KBr) 3100 and 3000 (C–H), 1720 and 1705 cm^{-1} (C=O); ^1H NMR δ = 1.42 (t, 6H, *J* = 6.9 Hz, CH_3-ester×2), 1.47 (s, 9H, *t*-Bu), 1.67 (t, 3H, *J* = 6.9 Hz, CH_3-ether), 2.72—2.89 (m, 2H, SCH_2), 3.61 (s, 2H, $ArCH_2$), 3.79 (s, 3H, OCH_3), 4.35—4.49 (m, 6H, CH_2O×3), 5.08 (q, 1H, CH), 5.39 (br-d, 1H, *J* = 7.9 Hz, NH), 6.83 and 6.85 (each d, 4H, *J* = 8.7 Hz, Ph), 7.85 (s, 1H, Th-5), 7.91 (s, 1H, Py-4), 8.17 and 8.33 (each s, 2H, Th-5×2); ^{13}C NMR δ = 14.2 and 14.3 (CH_3-ester×2), 14.3 (CH_3-ether), 28.1 (*t*-Bu), 35.9 ($ArCH_2$), 36.5 (SCH_2), 58.1 (CH), 55.1 (OCH_3), 61.4 and 61.5 (CH_2O-ester), 65.7 (CH_2O-ether), 80.1 (*t*-BuO), 113.9 (Ar-3,5), 120.7 (Th-5), 122.5 (Py-4), 129.4 and 129.5 (Th-5×2), 129.6 (Ar-1, Py-5), 130.0 (Ar-2,6), 139.4 (Py-2), 142.9 (Py-6), 146.8 and 148.1 (Th-4×2), 151.8 (Py-3), 152.5 (Th-4), 154.7 (CONH), 158.6 (Ar-4), 160.1 and 161.6 (Th-2×2), 165.0 and 165.2 (C=O×2), 169.9 (Th-2). Found: C, 54.55; H, 5.28; N, 8.08%. Calcd for $C_{37}H_{41}N_5O_8S_4$: C, 54.73; H, 5.09, N, 8.62%.

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